I hereby certify that this paper (along with any papers referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4).

Dated: July 1, 2011
Electronic Signature for Li-Hsien Rin-Laures: /Li-Hsien Rin-Laures Reg. 33,547/

Docket No.: 9189
(01017/40451B)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Brockhaus et al.

Application No.: 08/444,790 Art Unit: 1646

Filed: May 19, 1995 Examiner: Z. Howard

For: HUMAN TNF RECEPTOR

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. §§1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the enclosed document listed on the attached PTO/SB/08, which is an Office Action in a related application, U.S. Serial No. 08/444,791. No fee is due under 37 C.F.R. §1.97(e) because Applicants hereby certify that the document was mailed less than three months prior to the date of this information disclosure statement.

Applicant considers the issues raised in the enclosed office action ("Action") to be cumulative or irrelevant to the rejection presently pending in the current application. The primary obviousness rejection in the Action is based on the same combination of art at issue in the present case: Smith et al., U.S. Patent No. 5,395,760 (the "Smith patent") and Capon et al., U.S. Patent No. 5,428,130 (the "Capon patent"). See page 7 of Action.

The Action agrees that the Smith patent does *not* teach a fusion of p75 TNFR with an immunoglobulin (Ig) fragment where the Ig portion lacks the first domain of the constant region. Page 8, bottom. The Action relies on Capon's statement at col. 10, lines 18-20 that typically fusions retain "at least" functionally active hinge, CH2 and CH3 domains,

without addressing the Smith patent's explicit instruction that its fusions have "unmodified constant region domains" (col. 10, ln. 57). The Action also does not substantively address Capon's statements that a "preferred embodiment," as in the Smith patent, retains the entire constant region (the ligand binding partner being substituted for the variable region of an antibody, see col. 5, ln. 37-41 and col. 15, ln. 9-25). See also Capon at col. 10, lines 9-12: "Ordinarily, the ligand binding partner is fused C-terminally to the N-terminus of the constant region of immunoglobulins in place of the variable region(s) thereof." Thus, the obviousness rejection is defective because it failed to consider these statements and failed to explain why the ordinary skilled artisan would have been motivated to select the claimed species.

The Action also refuses to consider any of Applicants' evidence of unexpected results because (1) they are not a direct comparison to the purported closest prior art (page 12 of Action) and because (2) their practical significance is purportedly unclear (page 14 of Action). This is *clear legal error*. Moreover, it is contrary to the express instructions of the Manual of Patent Examination and Procedure (MPEP).

It is well settled that indirect comparative evidence is permitted and ***must*** be considered in making a determination of obviousness or nonobviousness and that absence of an expected property, in this case lack of effector functions, should be considered evidence of nonobviousness. MPEP §§ 716.02(b)(III) and 716.02(a)(IV). Evidence regarding properties of other TNF-binding immunoglobulin (Ig) fusion proteins is highly relevant to the required findings of "physical or chemical properties and utilities disclosed for the genus" in relation to the scope and content of the prior art under *Graham v. John Deere*. MPEP §2144.08. The Action cannot ignore evidence simply because it is not a direct comparison of the claimed invention to the purported closest prior art (for example, refusal to consider evidence regarding binding affinity and effector function of CD4-Ig fusions (Action, page 17, top), effector function of chimeric antibody molecules where TNF-binding murine regions are substituted for human variable regions (Action, page 17, top), the kinetic stability and TNF inhibition data in the Declaration of Dr. Lesslauer (Action, page 18, middle)).

Applicants provided evidence in the Declaration of Dr. Arora directly comparing embodiments of the claimed invention to embodiments that are *even closer* than

the purported closest prior art of the Smith patent. The Arora declaration contains results of a comparison to two different TNF-R/Ig fusions (Delta 57 and Protein 3.5D) that fall outside of the present claims because they are missing the first five amino acids of the hinge region, including a cysteine involved in disulfide bonding. They are similar to the claimed invention in that they (1) have the same homodimeric configuration, (2) are missing a CH1 domain and (3) are missing the light chain; yet, these homodimers retained effector function. This evidence clearly supports a finding that the lack of effector function seen with embodiments of the claimed invention was unexpected, yet the Action at page 12 ignored this evidence.

The asserted "unclear" practical significance of the unexpected results is also an inadequate reason to discount Applicants' evidence. Clearly the observation that etanercept has markedly reduced effector function was thought by researchers to be of practical significance since it was mentioned in several peer-reviewed articles by different groups of researchers. The Action does not dispute that the presence of effector functions, which kill cells that express antigen, is undesirable in some circumstances. A practical consequence of effector functions is the killing of cells that express TNF, and may be reflected in the monocytopenia (low monocyte count) observed in patients following treatment with anti-TNF antibody infliximab. See Furst et al. (2006), Semin. Arthritis Rheum. 36: 159-167, at page 164 (Document D2 on SB/08 filed March 29, 2011). It is notable that the package insert for infliximab (Remicade®) contains a black box warning regarding the risk of certain types of infections. See Wallis et al. (2004), Clin. Infect. Dis. 38: 1261-5, at page 1264 (Document D5 on SB/08 filed March 29, 2011).

In addition, the Action raises a number of issues that have no apparent relevance, such as the question of whether anti-TNF antibodies that have effector function "have clinical efficacy in diseases that etanercept cannot be used to treat" (page 13 of Action), or whether monovalent Fab fragments that are missing the Fc region and its associated effector functions are useful for treating disease "without side effects associated with Fc receptors or complement" (page 13 of Action). The Action cites a portion of a reference stating that "antibodies [with effector function] may also eliminate activated T-cells and monocyte/macrophages directly either by cell lysis or by inducing apoptosis" but asserts

that the risk of infection does not preclude use of anti-TNF antibodies (page 15 of Action). None of these statements have any relevance to whether the ordinary skilled person would have been motivated to select the claimed invention from among the multitude of possible species, subgenuses and genuses, or whether unexpected properties of the claimed invention render it nonobvious.

Finally, the Action attempts at page 18 to evade applicability of the Board's holding of nonobviousness in the present case, by merely adding the Smith patent as a third reference to the combination of Dembic and Capon. Such a rejection only delays prosecution, which is expressly contrary to the Patent Office's policy of compact prosecution (see, e.g., MPEP §2106(II)).

Dated: July 1, 2011

Respectfully submitted,

By: /Li-Hsien Rin-Laures Reg. 33,547/
Li-Hsien Rin-Laures
Registration No.: 33,547
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorney for Applicant